

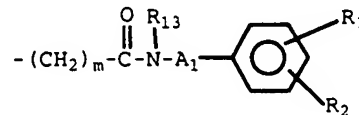
What is claimed is:

1. A diagnostic agent comprising an aminocarboxylate ligand complexed with a paramagnetic metal ion wherein a nitrogen atom within said
 5 aminocarboxylate is substituted with a substituted aromatic amide group.

2. The diagnostic agent of claim 1 wherein said substituted aromatic amide group is of the formula

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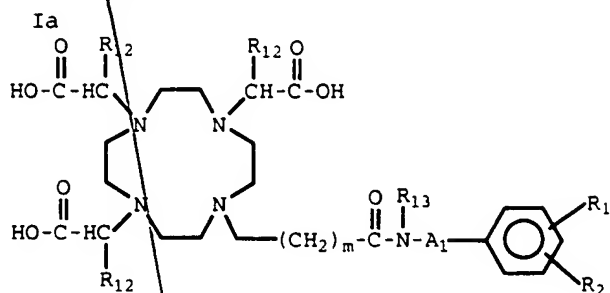
I



wherein

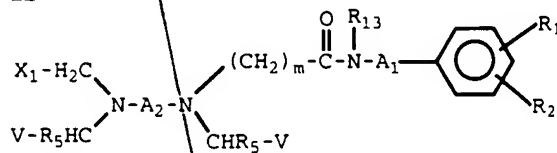
- A_1 is $-(CH_2)_{m'}$ - or a single bond;
 15 $(CH_2)_m$ and $(CH_2)_{m'}$ may independently be substituted with alkyl or hydroxyalkyl;
 R_1 and R_2 are each independently hydrogen, alkyl, $-NO_2$, $-NH_2$, $-NHCNHR_{12}$, NCS , $-C(=O)NR_3R_4$, NR_3COR_9
 where R_9 is alkyl or hydroxyalkyl, with the proviso
 20 that at least one of R_1 and R_2 must be other than hydrogen;
 R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;
 R_{12} is hydrogen, alkyl or hydroxyalkyl;
 25 R_{13} is hydrogen, alkyl, arylalkyl, alkoxy or hydroxyalkyl;
 m and m' are independently 1 to 5;
 and multimeric forms thereof.

3. A diagnostic agent of claim 2 wherein said ligand is of the formula



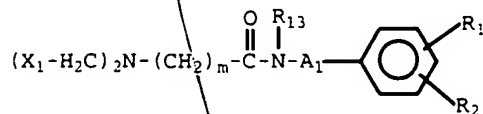
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Ib



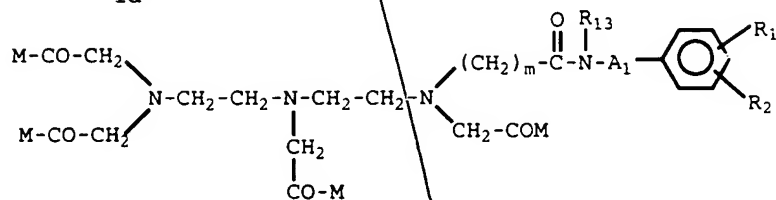
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Ic



15

Id



wherein m, R₁₃, A₁, R₁, R₂, and R₁₂ are as defined in claim 2 and wherein

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cont

5 X_1 is $-COOY_1$, PO_3HY_1 or $-CONHOY_1$;
 Y_1 is a hydrogen atom, a metal ion equivalent
 and/or a physiologically biocompatible cation of an
 inorganic or organic base or amino acid;

10 A_2 is $-CHR_6-CHR_7-$, $-CH_2CH_2(ZCH_2-CH_2)_n-$,
 $N(CH_2X_1)_2$ $CH_2-CH_2-N(CH_2X_1)_2$
 $-CH_2-\underset{\substack{| \\ N(CH_2X_1)_2}}{CH}-CH_2$ or $-CH_2-CH_2-\underset{\substack{| \\ CH_2-CH_2-N(CH_2X_1)_2}}{N}-CH_2-CH_2-$, wherein
 X_1 is as defined above;

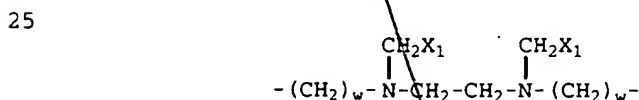
each R_5 is hydrogen or methyl;

15 R_6 and R_7 together represent a trimethylene
 group or a tetramethylene group or individually are
 hydrogen atoms, lower alkyl groups (e.g., 1-8
 carbons), phenyl groups, benzyl groups or R_6 is a
 hydrogen atom and R_7 is $-(CH_2)_p-C_6H_4-W$ -protein where p
 is 0 or 1, W is $-NH-$, $-NHCOCH_2-$ or $-NHCS-$, protein
 20 represents a protein residue;

n is 1, 2 or 3;

Z is an oxygen atom or a sulfur atom or the
 group NCH_2X_1 or $NCH_2CH_2OR_8$ wherein X_1 is as defined
 above and R_8 is C_{1-8} alkyl;

25 V is X_1 or is $-CH_2OH$, $-CONH(CH_2)_rX_1$ or $-COB$,
 wherein X_1 is as defined above, B is a protein or
 lipid residue, r is an integer from 1 to 12, or if
 R_5 , R_6 and R_7 are each hydrogen; then both V 's
 together form the group



where X_1 is as above, w is 1, 2 or 3, provided that
 at least two of the substituents Y_1 represent metal
 35 ion equivalents of an element with an atomic number
 of 21 to 29, 42, 44 or 57 to 83; from 1 to 4,
 advantageously 2 or 3, and preferably 2 M 's are $-OH$
 and the balance independently are $-OR_{10}$, $-NH_2$,

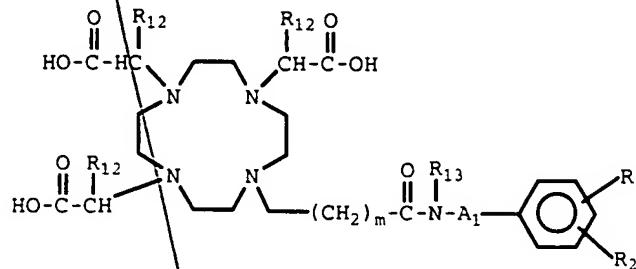
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-NHR₁₀ and/or NR₁₀R₁₀' wherein R₁₀ and R₁₀' are selected from an organic alkyl radical of up to 18 carbon atoms which may be substituted.

4. The diagnostic agent of claim 1 wherein
5 said paramagnetic metal ion is gadolinium.

5. A compound of formula Ia, Ib, Ic or Id as defined in claim 3, including multimers thereof.

6. A compound of the formula



wherein

A₁ is -(CH₂)_{m'}- or a single bond;

(CH₂)_m and (CH₂)_{m'} may independently be
15 substituted with alkyl or hydroxyalkyl;

R₁ and R₂ are each independently hydrogen,

alkyl, -NO₂, -NH₂, -NHCNHR₁₂, NCS, -C(=O)-NR₃R₄ and
NR₃COR₉ where R₉ is alkyl or hydroxyalkyl, with the
proviso that at least one of R₁ and R₂ must be other
20 than hydrogen;

R₃ and R₄ are independently hydrogen, alkyl,
arylalkyl, aryl, alkoxy and hydroxyalkyl;

R₁₂ is hydrogen, alkyl or hydroxyalkyl;

R₁₃ is hydrogen, alkyl, arylalkyl, aryl,
25 alkoxy or hydroxyalkyl;

m and m' are independently 1 to 5;

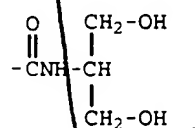
and multimeric forms thereof.

7. A compound of claim 6 wherein R_1 and R_2 are each $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{NR}_3\text{R}_4 \end{array}$ wherein each R_3 group is hydroxy-alkyl.

8. A compound of claim 6 wherein R_1 and R_2 are each $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{NR}_3\text{R}_4 \\ | \\ -\text{CH}_2-\text{CH}-\text{CH}_2\text{OH} \\ | \\ \text{OH} \end{array}$ wherein each R_3 group is selected from $\begin{array}{c} \text{OH} \\ | \\ -\text{CH}(\text{CH}_2\text{OH})_2 \end{array}$ and $-\text{CH}(\text{CH}_2\text{OH})_2$, and wherein each R_4 group is hydrogen.

9. A compound of claim 6 wherein R_1 and R_2 are each $\begin{array}{c} \text{O} \quad \text{OH} \\ \parallel \quad | \\ -\text{CNHCH}_2-\text{CH}-\text{CH}_2-\text{OH} \end{array}$.

10. A compound of claim 6 wherein R_1 and R_2 are each



11. A compound of claim 6 having the name 10-[2-[[3,5-bis[[2,3-dihydroxypropyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

12. The gadolinium complex of the compound of claim 11.

13. A compound of claim 6 having the name 10-[2-[[3,5-bis-[[2-hydroxy-1-(hydroxymethyl)-ethyl]amino]carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

14. The gadolinium complex of the compound of claim 13.

15. A compound of claim 6 having the name 10-[2-[methyl[3,5-bis[[2-methylbutyl)amino]-

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carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

16. The gadolinium complex of the compound of claim 15.

5 17. A compound of claim 6 having the name 10-[2-[[4-[[2,3-dihydroxypropyl]amino]carbonyl]-phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

10 18. The gadolinium complex of the compound of claim 17.

19. A compound of claim 6 having the name 10-[N-(4-nitrophenyl)acetamido]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

15 20. The gadolinium complex of the compound of claim 19.

21. A compound of claim 6 having the name 10-[N-(4-aminophenyl)acetamido]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

20 22. The gadolinium complex of the compound of claim 21.

23. A compound of claim 6 having the name 10-[[N-(4-(N'-isothiocyanato)phenyl)acetamido]]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

25 24. The gadolinium complex of the compound of claim 23.

25. A compound of claim 6 having the name 10-[N-[4-(N'-methylthioureido)phenyl]acetamido]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

30 26. The gadolinium complex of the compound of claim 25.

27. A compound of claim 6 having the name 10-[N-[4-(N',N'-diethylaminothioureido)phenyl]acetamido]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

28. The gadolinium complex of the compound of claim 27.

29. A compound of claim 6 having the name 10,10'-[[[(1,2-ethanediyl)diimino]bis(thioxomethyl)-
5 diimino]bis(4,1-phenylene)]diimino-bis[1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid].

30. The gadolinium complex of the compound of claim 29.

31. A compound of claim 6 having the name
10 10,10'-[[[(Thioxomethyl)bis(imino)bis(4,1-phenylene)]bis(imino)]bis(2-oxo-2,1-ethanediyl)]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

32. The gadolinium complex of the compound of claim 31.

15 33. A compound of claim 6 having the name 10,10',10''-[[[[[iminobis(2,1-ethanediyl)triimino]-tris(thioxomethyl)]-triimino]tris-(4,1-phenylene)]-triimino]tris(2-oxo-2,1-ethanediyl)]tris[1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid].

20 34. The gadolinium complex of the compound of claim 33.

35 A compound of claim 6 having the name 10-[2-[[2-(4-nitrophenyl)ethyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

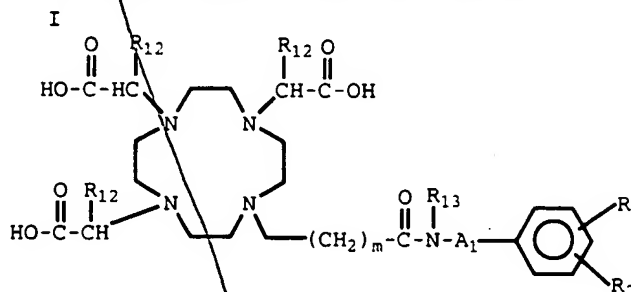
25 36. The gadolinium complex of the compound of claim 35.

30 37. A compound of claim 6 having the name 10-[2-[[3,5-bis([(2-hydroxyethyl)amino]-carbonyl)-phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, monosodium salt.

38. The gadolinium complex of the compound of claim 37.

Sub A 21

39. A complex, or a pharmaceutically acceptable salt of a complex, of a metal atom and a metal chelating ligand having the formula



wherein

A_1 is $-(CH_2)_{m'}$ - or a single bond;

$(CH_2)_m$ and $(CH_2)_{m'}$ may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

alkyl, $-NO_2$, $-NH_2$, $-NHC(=S)NR_{12}$, NCS , $-C(=O)NR_3R_4$ and NR_3COR_9 where R_9 is alkyl or hydroxyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R_{12} is hydrogen, alkyl or hydroxyalkyl;

R_{13} is hydrogen, alkyl, arylalkyl, aryl,

alkoxy or hydroxyalkyl;

m and m' are independently 1 to 5;

and multimeric forms thereof

40. A complex of claim 39 wherein R_1 and R_2

are each $-C(=O)NR_3R_4$ wherein each R_3 group is hydroxy-alkyl.

41. A complex of claim 39 wherein R_1 and R_2 are each $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{NR}_3\text{R}_4 \\ | \\ \text{OH} \end{array}$ wherein each R_3 group is selected from $-\text{CH}_2-\text{CH}-\text{CH}_2-\text{OH}$ and $-\text{CH}(\text{CH}_2\text{OH})_2$, and wherein each R_4 group is hydrogen.

5 42. A complex of claim 39 wherein R_1 and R_2 are each $\begin{array}{c} \text{O} \quad \text{OH} \\ \parallel \quad | \\ -\text{CNHCH}_2-\text{CH}-\text{CH}_2-\text{OH} \end{array}$

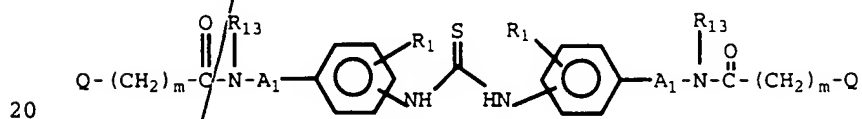
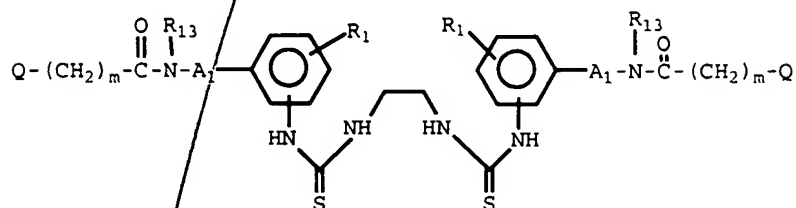
43. A complex of claim 39 wherein R_1 and R_2 are each

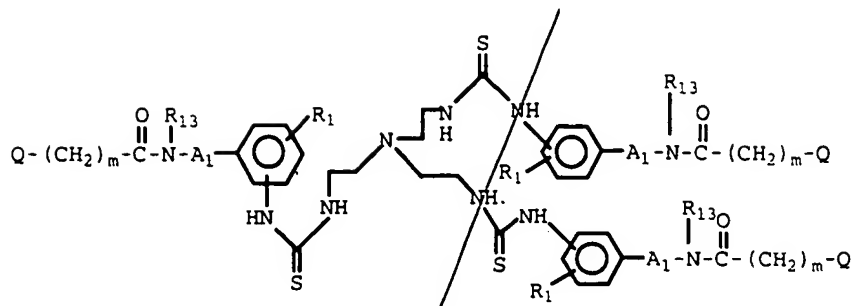


44. A complex of claim 39 wherein said metal atom is of atomic number 56-83.

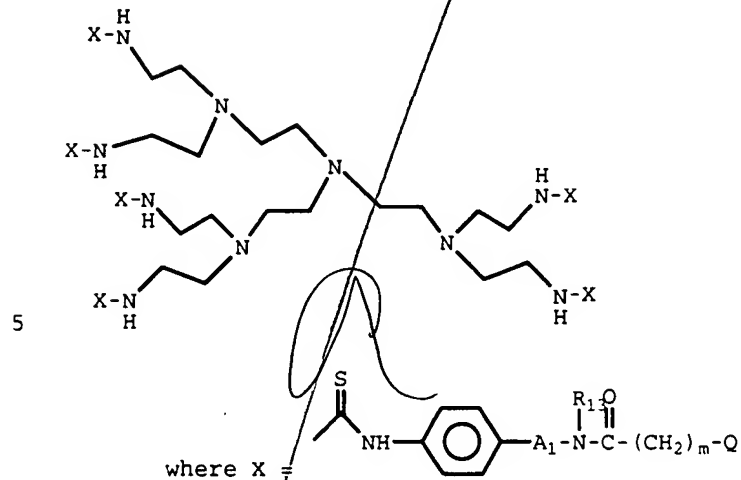
15 45. A complex of claim 39 wherein said metal is gadolinium(III).

46. A multimer selected from





or



10 and wherein Q is an aminocarboxylate ligand and the other variables are as defined in claim 3.

47. A compound of claim 6 having the name 10-[2-[[3,5-bis[[[(2-methylbutyl)amino]carbonyl]-phenyl]amino]2-oxoethyl]1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

15 48. The gadolinium complex of the compound of claim 47.

49. A compound of claim 6 having the name 10,10',10'',10''',10'''',10''''-[[[[[[[[(Nitrilo-

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tri-2,1-ethanediyl)tris(nitrilo)hexakis-(2,1-ethane-
diyl)hexakis(imino)hexakis-(carbonothioyl)hexakis-
(imino)hexakis-(4,1-phenylene)hexakis-(imino)-
hexakis-(2-oxo-2,1-ethanediyl)hexakis[1,4,7,10-tetra-
5 azacyclododecane-1,4,7-triacetic acid].

50. The gadolinium complex of the compound of
claim 49.